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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,888	06/26/2001	Jean Fernand Armand Lacrampe	JAB-1626	4721

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EXAMINER
BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/02/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/891,888	LACRAMPE ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 0203* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12 and 23-30* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☒ Claim(s) *23-27* is/are allowed.

6)☒ Claim(s) *29* is/are rejected.

7)☒ Claim(s) *30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/11/2003 has been entered.

Upon entering the amendment claims 11-12 and 23-30 are in the case. Of which claims 11-12 were withdrawn from consideration as noted in paper # 6.

Claims 23-30 are now active in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Process claim 28 is indefinite as it recites, "paragraph a" which is vague and confusing. Its replacement with step a) or process a) is suggested.
2. Process claim 28 is also indefinite as it recites, "converting compound of formula I into each other following art known transformations". It is unclear what is

converted to what and how. This is a process claim and steps involved should be recited positively to know the scope of the patent protection sought.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for non-reactive variable groups that do not participate in the reaction, does not reasonably provide enablement for all reactive variables groups such as those recited below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to a 1,2-4-triazine compound, process of making and method of use. However, specification is not adequately enabled to make compound of claim

1 where R^5 is a haloalkyl group. Process claim 28 recites in a) a process of reacting compound of formula II with H-X-R^2 to displace W^1 which is a leaving group. But if R^5 is a haloalkyl group, it will also undergo displacement reaction with halo group functioning as leaving group. Specification has no teaching as to how to perform this reaction without displacing halo in R^5 when R^5 is a haloalkyl group.

Specification is also not adequately enabled to make compound using the process b). Note it is not clear how the process of elimination of "E" group is to be performed for example if it s a cyano or alkylsulfonyloxy group. Also note the E group is not limited what is recited in the specification and it is not clear how one will be able to perform such transformation when reactive groups such as haloalkyl etc were present in the reactants.

Specification is also not enabled to make compound of formula I using the process c) where R^2 is, as recited in claim 1, an aryl, Het^1, cycloalkyl and alkyl group. Note H-R^2 would be hydrocarbon group and there is no teaching in the specification that show the reaction of a hydrocarbon with a carbonyl group of compound X as claimed in process c.

Process d of claim 10 recites alkylation of the hydroxyl of compound Ia-2 but the groups R^2, R^4 and R^5 are also permitted to have hydroxyl substituents. Specification has no teaching or suggestion as to how would one selectively alkylate the hydroxyl of compound X without alkylating the hydroxyls in R^2, R^4 and R^5.

Process e) which involves replacement of hydroxyl of compound Ia-2 by halogen also poses the same problem outline in reason # 4. Specification has no teaching

as to how to perform this reaction without affecting hydroxyl elsewhere in the molecule. See R^2, R^4 and R^5 substituents.

Reason # 1 also apply to process f) and process g) both of which recite nucleophilic displacement of halo or leaving group W^4 which are also present in the R^2, R^4 and R^5 groups.

Similarly, process h) recites acylation of amino group of compound of formula XIV but R^4 and R^5 groups are also permitted have amino groups which may undergo the same acylation. Specification has no teaching as to how to selectively acylate the said amino group of compound of formula XIV without acylating R^4 and R^5 groups to make compounds bearing amino groups in R^4 and R^5 groups. The same applies to process n) where acylation is recited and process o) where an N-alkylation is recited.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the process of making compounds when reactive substituents or chemically incompatible substituents are present in the starting material.

4. The presence or absence of working examples:

Although examples in the specification show several compounds, there are no representative examples showing the viability of the process for plurality of reactive substituents as noted above embraced in the instant claims.

5. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language could be prepared by the process and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward during reaction given the fact that the reactions involve the same functional group transformations.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula I embraced in the instant claims in view of the process requirement to use same reactive functional groups as reactants as end products.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bronchial asthma, atopic dermatitis,

allergic-rhinitis or allergic conjunctivitis and treatment of related tumor and retinopathy, does not reasonably provide enablement for any or all conditions / diseases including those yet to be discovered as due eosinophil-dependent inflammatory diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim is drawn to "treating eosinophil-dependent inflammatory diseases" .The scope of the claims includes not only any or all conditions/diseases but also those condition yet to be discovered as due to "eosinophil-dependent inflammatory diseases" for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at page 60. The instant compounds are disclosed to have inhibitory activity toward eosinophil-dependent inflammation which relates to inhibition of IL-5 and it is recited that the instant compounds are therefore useful in treating any or all conditions, for which applicants provide no competent evidence. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of inflammatory diseases are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently

unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Mishra et al. Journal of Immunology, 2464-2469, 2002, suggests that current status of inhibitors of eosinophil-dependent inflammation due to IL-5 is at best exploratory and needs further experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating eosinophil-dependent inflammation inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the eosinophil-dependent inflammatory diseases due to IL-5 are unpredictable and are still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibitors of eosinophil-dependent inflammation are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to eosinophil-dependent inflammation.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme(receptor)-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having

ordinary skill in the art would have to perform an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowable Subject Matter

Claims 23-27 are allowed. Claim 30 is objected to as being dependent upon a rejected base claim 29, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims would be allowed since specific species and composition embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

5/31/2003